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MNDO CALCULATIONS OF THE EFFECTS OF SUBSTITUTION ON ANTIOXIDANT ACTIVITY OF PHENOLS AND VITAMIN E

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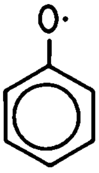
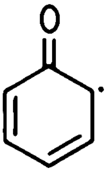
Abstract - MNDO calculations are reported for the O-H bond dissociation energy in phenol and -OH, $-CH_3$, and $-NH_2$ substituted phenols. The phenol dissociation energy agrees well with the experimental result, as does the change due to a para -OH group; the agreement is less good for methyl substitution. The effect of rotating the O-H substituent out of the benzene plane is explored and analyzed, and the calculations are related to corresponding effects in Vitamin E chemistry.

Recently Burton and Ingold have established that Vitamin E does in fact function very effectively as a chain-breaking phenolic antioxidant, and have made rate measurements and speculated about the relative antioxidant effectiveness of related systems (1). Much of their argument is based upon the thermochemical properties of substituted phenoxy radicals, as determined from relative rate constant measurements by Mahoney and DaRooge (2). We have re-explored this problem by means of molecular orbital calculations, a procedure which allows one to determine quantities which are experimentally inaccessible and can give further insight into the problem. In particular, we have executed MO calculations using the semi-empirical MNDO method of Dewar and coworkers (3); in the case of free radicals, the "half-electron" method version of this theory was employed. This technique is sufficiently efficient that one can afford to optimize all bond lengths and most of the bond angles in systems the size of substituted phenols and phenoxy radicals. (The only assumptions we made are that the CCH angles are 120° and that all atoms are coplanar, except of course for the H atoms of methyl and amino substituents and of the -OH group when twisted.)

MNDO calculations for the phenoxy radical itself yielded a pi electronic state, with rather non-uniform CC distances as compared to phenol and benzene. The 1,2 and 1,6 bonds are rather long, 1.488Å, the 2,3 and 5,6 bonds are rather short at 1.378Å and the 3,4 and 4,5 bonds intermediate at 1.423Å. The C-O bond at 1.234Å is contracted almost to the double bond value (1.227Å in acetone), compared to 1.358Å for phenol itself. Thus MNDO predicts significant delocalization of the unpaired pi electron around the ring, primarily at the ortho and para positions. This is consistent with substantial resonance between the dominant valence-bond structure a and structures b, c and d. The O-H bond dissociation energy calculated for phenol is 88.7 kcal mol^{-1}, in excellent agreement with the experimental value of 88.3 (2). The calculated spin densities are 0.234e at the ortho carbons, 0.361e at the para and only 0.138e at the oxygen (indicating that in importance structure d > b, c > a).


a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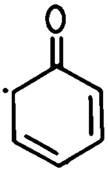
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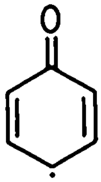
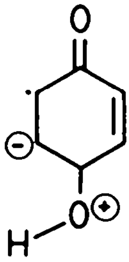

d

The geometries for phenol and the phenoxy radical were re-optimized in each case to incorporate the effect of a coplanar -OH substituent at either the ortho, meta or para carbon. The O-H bond energy changes by -3.39, +1.79 and -3.84 kcal mol^{-1} respectively; again agreement with experiment is very good since Mahoney and DaRooge found that the bond energy in the meta-substituted phenol is 2.6 kcal mol^{-1} greater than in phenol, and that in the para isomer is 3.7 kcal mol^{-1} less than in phenol (2). The additional stabilization of the phenoxy radical by an ortho or para hydroxyl group results, as expected, from contribution of some oxygen lone pair density into the phenoxy pi system. In particular, the para oxygen loses 0.144e into the pi system, almost half of which is captured by that carbon meta to O which is closer to the hydroxyl hydrogen (see structure e). The delocalization of the pi electrons of the para-OH group is less inhibited in the electron-poor radical than it is in the electron-rich 1,4 dihydroxyphenol. (The substitution of a para OH group into phenol is slightly less favourable energetically than the substitution of OH in benzene, according both to experiment and to MNDO results.) Thus the O-H dissociation energy is reduced by a para hydroxyl group.


e

In contrast to the excellent results achieved for hydroxy-substitution, MNDO calculations for methyl substitution are disappointing. Para substitution of -CH_3 for hydrogen is predicted to reduce the O-H bond energy by only 0.64 kcal mol^{-1}, compared to 1.8 experimental (2). To determine the effect of substituting a methyl group for the hydrogen within the OH substituent, we performed MNDO calculations to evaluate the O-H bond dissociation energy in trans-2-hydroxy- and 2-methoxy-vinyl alcohol. (MNDO calculations for the benzene derivatives themselves would have been too expensive computationally.) The methyl group here is predicted to raise the dissociation energy by 0.6 kcal mol^{-1} in contrast to the 0.6 kcal mol^{-1} decrease observed experimentally (2). We also performed calculations on a para-NH_2 substituted phenol, since it is anticipated that amino substitution should be more effective even than hydroxyl in stabilizing the radical. For a planar para NH_2 group, the calculated dissociation energy is 2.8 kcal mol^{-1} less than that for para-OH substitution. Unfortunately, devising a real cyclic analog of Vitamin E in which the geometry at N allows conjugation to the benzene ring is difficult (4a).

Ingold has made some interesting observations with respect to the effect on the O-H bond dissociation energy in phenols and phenolic biological molecules such as Vitamin E of non-coplanarity of the para-substituted -OR group with the benzene ring (4). To study this effect theoretically, we have performed MNDO calculations on both para-hydroxyphenoxyl radical and 1,4-dihydroxybenzene with the para OH group twisted away from the benzene ring to varying extents. Interestingly, of the 3.84 kcal mol^{-1} stabilization in the planar form, only 2.4 kcal mol^{-1} is lost when a full twist of 90 degrees is made. The residual stabilization of 1.3 kcal mol^{-1} in the twisted form is due mainly to the delocalization into the ring's pi system in the radical of 0.049e from the sp^3 lone pair of the OH group which now overlaps well with the pi AO on the para carbon. Because of the conjugative participation of two inequivalent oxygen lone pairs, the potential function for rotation is somewhat complicated. However, for angles up to about 40°, the energy loss due to twisting the CC-OH dihedral angle is approximately proportional to $1 - \cos \phi$. Since the proportionality constant for twisting in the dihydroxybenzene is about half the 6.4 kcal mol^{-1} value for the radical, the change to the dissociation energy is approximately $3.2\ (1-\cos \phi)$. Clearly the equilibrium twist angle in the radical will be less than that in the dihydroxy compound, since twisting is more expensive in the former.

According to X-ray diffraction structures of 4-alkoxyphenols (1), the Ar-O-H dihedral angles are usually non-zero and range from 5° to 60°. We investigated the effect of twisting about both C-O bonds simultaneously in 1,4-dihydroxybenzene and find that the cost in energy is very close to twice that for twisting about one bond only. Thus the dissociation energy of a di-twisted 1,4-OH substituted phenol is virtually identical to that for a completely planar system, since the destabilization in the radical is matched by that in the neutral system.

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